REMARKS

This submission is made further to the Notice of Withdrawal From Issue Under 37 C.F.R. 1.131(b) dated July 31, 2001. Reconsideration of this reissue application, in view of the above amendments and the following remarks, is respectfully requested. Pursuant to 37 C.F.R §1.173(b)(ii), the status of all patent claims and all added claims is as follows:

Original patent claims 1 and 2 are pending. Claims 3-20, added in the Preliminary Amendment dated March 6, 1998, have been cancelled. Claims 21-30, added in the Amendment dated May 24, 2000, are pending. Claim 31, added by this amendment, is pending. Thus, claims 1-2 and 21-31 are pending and at issue.

Claims 1, 2 and 26 have been amended by this amendment to more particularly recite and specifically set forth what applicant regards as the invention. Specifically, claim 1 has been amended to delete the recitation of the hapten dinitrophenyl (DNP). This amendment is supported at column 3, lines 58-59, and by claim 1, of the original patent.

Original claim 2 and new claim 26 have been amended to recite that the vaccine or administration of said vaccine induces a delayed-type hypersensitivity (DTH) response against unmodified melanoma cells. This amendment to claims 2 and 26 is fully supported by the specification, *e.g.*, at column 3, ll. 8-13; column 4, ll. 29-35; and column 6, ll. 50-53.

New claim 26 has been amended to delete the recitation of cryopreserved cells. This amendment is supported by the specification at, *e.g.*, column 1, lines 13-16, by way of contrast to 46-48 (optional cryopreservation).

New claim 31 recites more particular optional features of the invention as set forth in the specification, *e.g.*, compare column 1, lines 13-16 to lines 46-48 (optional cryopreservation).

As amended, the claims are further distinguished from the teachings of the reference by Berd et al. (Proc Am Ass Cancer Res 1989;30:382; hereinafter "Berd Abstract") submitted with the Reissue Request filed March 6, 1998. The lack of teachings in the Berd Abstract with respect to the claimed invention is discussed below and in the accompanying Braun Declaration.

The Berd Abstract

The Berd Abstract reports preliminary results of a melanoma patient study conducted using a vaccine consisting of autologous melanoma cells conjugated to DNP. The Abstract describes an inflammatory response being developed in tumor masses of 3 out of 4 patients after administration of DNP-conjugated cells, and that in one patient, some tumors were beginning to regress and a biopsy showed infiltration of CD4+ and CD8+ T lymphocytes. The 3 patients showing an inflammatory response in tumor masses also developed a DTH-response to DNCB and DNP-conjugated autologous lymphocytes.

Importantly, the Berd Abstract fails to teach or suggest that the DNP-vaccine could elicit a DTH-response was against ***unmodified*** tumor cells. Instead, the Abstract merely reports a confirmed DTH-response to DNCB and DNP-conjugated autologous lymphocytes (2nd last sentence of abstract), and that only a vaccine based on unmodified tumor cells induced a DTH-response against unmodified tumor cells (1st sentence of abstract). Consequently, the Berd Abstract fails to convincingly establish that ***any*** immune response against melanoma tumor cells in the subject had been evoked, whether against unmodified or DNP-haptenized cells. Without any indication that a specific immune reaction towards unmodified melanoma cells, or at least melanoma cells in some form, was induced by DNP-modified tumor cells, a person skilled in the art could assume that the observed inflammatory response only was a non-tumor specific consequence of BCG injection (Braun Declaration, ¶11). A mere hapten-specific immune response as reported in the Berd Abstract (the DTH response to DNCB and DNP-conjugated lymphocytes) could not contribute to any long-term clinical benefit and would not, for example, protect against recurrence of the cancer. Accordingly, no successful ***tumor-specific*** immuno-therapeutic method, as set forth by the amended claims, is taught or suggested by the Berd Abstract.

The teachings of the Berd Abstract are restricted to vaccines made from DNP-conjugated melanoma cells, and absent some evidence of success, cannot be deemed to extend to other haptens that could be used instead of DNP. Thus, it lacks any suggestion that other haptens, such as those recited in amended claim1, TNP and

N-iodoacetyl-N'-5 sulfonic 1-naphtyl ethylene diamine, could be used in the same context. Since the Berd Abstract only reports that a hapten-specific response was elicited, a person of skill in the art could not have expected that a response to TNP would be elicited from TNP-conjugated melanoma cells, much less that a vaccine based on TNP-conjugated melanoma cells would induce a response against non-haptenized melanoma cells.

The Berd Abstract mentions nothing about using cryopreserved cells, and does not suggest that such cells could be used. Claim 31 calls for cryopreserved cells, as described in the specification at column 3, lines 44-48.

Also, as set forth by the Braun Declaration accompanying this response, the Berd abstract is silent with respect to administration route of the vaccine, a crucial parameter for evaluating the teachings of this report (Braun Declaration ¶9 and ¶11). Claims 2 and 26 recite that intradermal administration of the haptenized melanoma cells elicits a DTH-response against unmodified melanoma cells, a strategy not disclosed or suggested by the Berd Abstract. The Berd Abstract does not teach which injection route results in an anti-hapten response, and could therefore not provide any guidance as to which strategy would result in a response against unmodified cells.

The Berd Abstract does not describe a successful immunotherapy for melanoma (Braun Declaration, ¶7). On the contrary, it represents a preliminary result that raises more questions and ambiguities than it answers. Early animal work on tumor immunotherapy could not establish whether similar approaches could work in

humans (Braun Declaration, ¶8). The Abstract fails to provide a definitive protocol that would permit one to repeat the work, or establish that it achieved any clinical benefit (Braun Declaration, ¶¶9-11). That hapten-specific responses could be elicited by haptenized cells was not surprising given the skill in the art at the time of the invention, but that any response to unmodified melanoma cells could be induced by haptenized cells, as recited in amended claims 2 and 26, could not have been anticipated or expected at the time of the invention (Braun Declaration, ¶10).

Therefore, in view of the foregoing amendments and remarks, it is respectfully requested that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

Paul F. Fehlner, Ph.D.
Reg. No. 35,135
Attorney for Applicants

DARBY & DARBY, P.C.
805 Third Avenue
New York, N.Y. 10022
Phone (212) 527-7700
AL1199.WPD